

ELECTROCARDIOGRAPHIC EFFECTS OF ANTIMONY DIMERCAPTO-SUCCINATE ('ASTIBAN')

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Hitherto the most effective drug available in the treatment of schistosomiasis has been sodium antimony tartrate (SAT), a trivalent antimony compound. SAT has to be administered by the intravenous route and the usual course of treatment lasts from 2 to 3 weeks. It is a toxic drug and may cause unpleasant side effects including nausea and vomiting, diarrhoea, fever, muscle and joint pains, skin rashes, hepatitis and headache. In addition SAT produces toxic effects on the myocardium. Honey (1960) has reviewed publications on the electrocardiographic effects of the trivalent antimony compounds, SAT, potassium antimony tartrate (tartar emetic), stibophen ('fouadin') and anthiomaline. These reports confirm that trivalent antimony compounds almost always produce electrocardiographic changes. The earlier of these reports (Beaser *et al.*, 1946; Schroeder *et al.*, 1946; Tarr, 1947) recorded standard leads and CF₄ only. Later reports (Suarez *et al.*, 1948; O'Brien, 1959; Honey, 1960) describe changes recorded in standard, limb and chest leads. Despite differences in treatment and electrocardiographic leads there is basic agreement about changes in the S-T segment and T wave.

In evaluating the efficacy of a new trivalent antimony preparation, antimony dimercapto-succinate ('astiban') synthesized by Dr. Ernst A. H. Friedheim of New York for the treatment of schistosomiasis, we made a particular study of electrocardiographic effects. We report our findings in a series of 34 patients who received a single course of the drug. 'Astiban' (F. Hoffman-La Roche & Co.) has the structure of a complex polyvalent acid, which may form salts with a great variety of cations. The chemotherapeutic activity is a function of its antimony content. Comments on clinical reports of its use in the treatment of schistosomiasis *hæmatobium*, *mansoni* and *japonicum*, are generally favourable (Friedheim *et al.*, 1957; Alves, 1959; Salem *et al.*, 1957; Okabe *et al.*, 1959) judging from the cure rate and minor side effects compared with other antimonials. The brevity of the treatment and the administration by the intramuscular route are of special importance in connection with mass treatment.

To our knowledge no special studies have been made of the electrocardiographic effects of this new antimonial although Friedheim *et al.* (1957) briefly mention insignificant and reversible T wave changes in 10 South American patients.

METHOD

A total of 34 patients were admitted to the trial of whom 32 were male and 2 female, with ages ranging from 12 to 50 years. All the patients were African, 30 were Nilotic and hailed from the Northern Province of Uganda which is an endemic schistosomiasis area, and 4 patients were Bantu. *Schistosomiasis mansoni*

had been diagnosed during routine investigation of a variety of abdominal pains and diarrhoea and the majority of patients were otherwise healthy policemen and well fed prisoners. None of them were anæmic and each was carefully examined on admission with particular attention to the cardiovascular and hepatic systems.

Each patient received a 2 G course of 'astiban' in 5 equal doses by daily intramuscular injection. A 12 lead electrocardiogram was taken on admission, immediately after the cessation of therapy, and in 10 instances on a third occasion between ten days and six weeks after cessation of treatment. A direct writing Cambridge electrocardiograph was used throughout. The tracing was calibrated in the usual manner and the tracings were taken by the same technician with the patient lying in the semi-recumbent position. Apart from vitamin K for liver biopsy, none of the patients received any treatment other than 'astiban' and they remained quietly at rest, but not in bed. The effectiveness of treatment will be reported elsewhere (Rosanelli, 1961, in preparation).

RESULTS

Of the 34 patients admitted to the trial 8 were excluded since observations were incomplete, leaving 26 patients in the study. The majority exhibited sinus arrhythmia either before or after treatment or on both occasions. One patient exhibited occasional atrial ectopic beats after treatment. No other arrhythmias were recorded. In 19 patients there was no significant change in heart rate

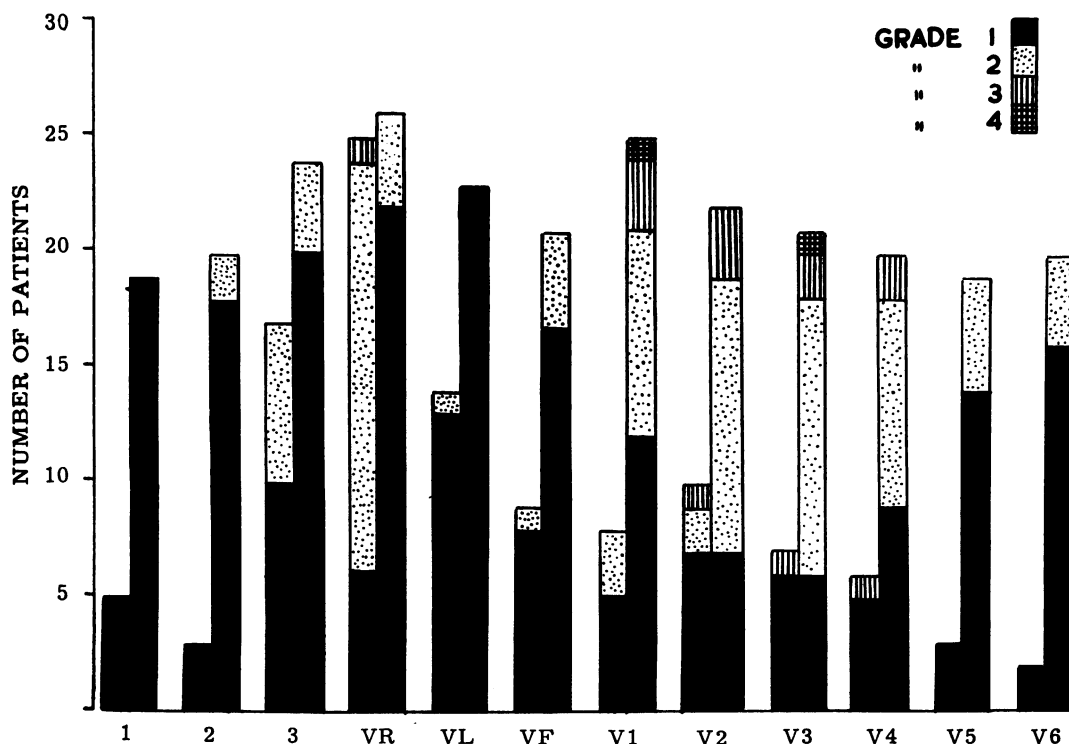


Fig. 1.—T wave changes before and after treatment in 26 African patients.

(up to 10 beats). In 5 there was an increase and in 2 a decrease in the heart rate. Bifid P waves, not exceeding the normal limit of 0.12 sec. duration or 2 mm. in height were observed in 1 or more leads in 16 patients before treatment, persisting in 13 of them after treatment. The P-R interval did not exceed the normal limit of 0.22 sec. in any patient with the exception of one in whom a pre-treatment P-R interval of 0.20 sec. increased to 0.22 sec. in the post-treatment tracing. The voltage and

duration of the QRS complex was normal in all patients before and after treatment. One patient exhibited an incomplete right bundle-branch block pattern, which remained unchanged after treatment. A number of patients showed S-T segment elevation in one or more chest leads particularly in leads V_2 and V_3 , and the pattern after treatment was the same.

The most significant changes following treatment were observed in the T wave and we divided them into 4 grades. Minimal changes (grade I) consisted in reduction of T wave amplitude amounting to flattening without inversion. Slight changes consisted in inversion of T wave by 1 mm. or less. Moderate changes (grade III) consisted in inversion of T waves up to 2 mm. and biphasic T waves. Severe changes (grade IV) consisted in T wave inversion in excess of 2 mm. The frequent occurrence of elevated S-T segments in the chest leads did not interfere with assessment of the terminal portion of the S-T segment or of the T waves. Fig. 1 shows the extent and severity of T wave changes before and after treatment. Assuming that minor degrees of T inversion may occur normally in leads III, VR and to a lesser degree in V_1 , it will be noted that the maximum incidence and most obvious change in T occurred in leads V_2 , V_3 and V_4 . Lesser degrees of T changes were observed in V_5 and V_6 and also in leads I and II. In 10 patients in whom post-treatment electrocardiograms were taken, there was a complete return to pre-treatment patterns between 10 days and 6 weeks following the cessation of treatment.

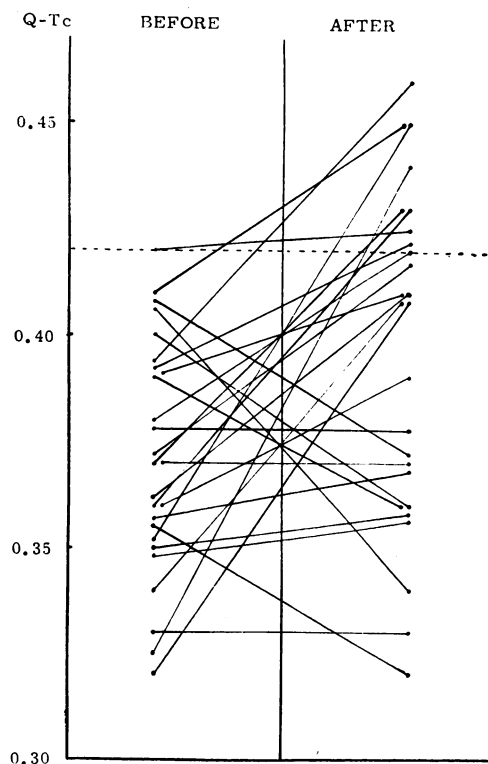


Fig. 2.—Q-Tc in 26 patients before and after treatment with 'astiban'.

The Q-Tc was determined after the formula of Bazett (1920) as modified by Taran and Szilagyi (1947). The results in 26 patients are shown in Fig. 2. A prolongation of Q-Tc was demonstrated in 18 patients, in 3 no change occurred, and in 5 there was a decrease. In 10 patients post-treatment Q-Tc estimations showed a value of 0.42 sec. or more. It was noticed that in 15 of the 18 patients showing prolongation of Q-Tc, the change correlated with the more severe degrees of T changes

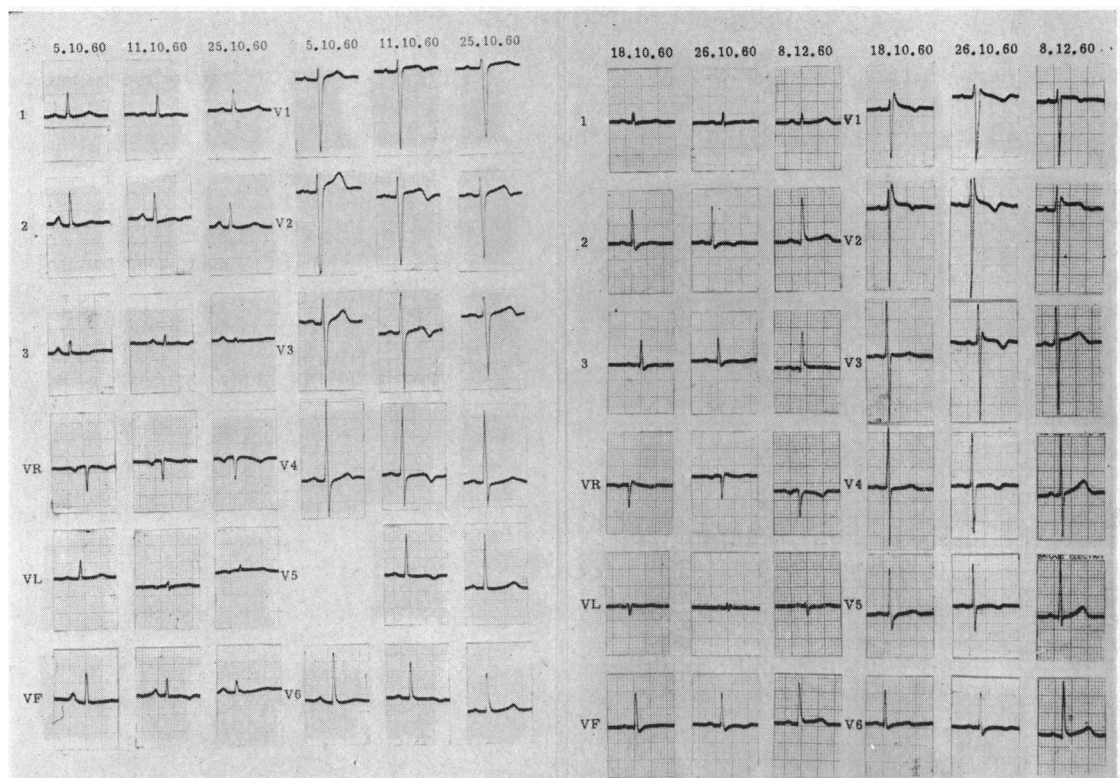


Fig. 3 and 4—Serial electrocardiograms from 2 patients taken before, during, and after treatment with 'astiban'.

suggesting a direct relationship between the one and the other. In Fig. 3 and 4 are shown serial tracings obtained from two patients with pronounced electrocardiographic changes during treatment with 'astiban' reverting to normal after cessation of treatment. Despite electrocardiographic changes, no patients developed any symptoms or signs of cardiac involvement.

DISCUSSION

Because of its ease of administration and low incidence of toxic effects 'astiban' represents an advance in the antimonial treatment of schistosomiasis. Our particular concern in this study was to evaluate the electrocardiographic effects of 'astiban', since other trivalent antimonial compounds produce electrocardiographic changes in nearly all patients (Honey, 1960).

We report lower incidence and severity of electrocardiographic changes compared with Honey's findings with SAT. If we regard the pre-treatment electrocardiogram as the patient's normal and consider that a change in the post-treatment tracing is evidence of the toxic effects of 'astiban', we conclude that the only important changes occurred in the T wave. Excluding normal variations in the T wave, e.g. inversion of the T wave in III, VR and V₁ (Wood, 1956), and minor degrees of flattening in the pre-treatment tracings, the highest incidence of T changes occurred in left ventricular leads and leads I and II accounting for between 14 to 18 instances of T changes in varying leads in the total of 26 patients studied. Severe changes occurred in only 2 instances. Generally, minor changes were recorded in leads I and II and minor or moderate changes in the chest leads, and they were transient, disappearing in 10 days to six weeks after cessation of therapy.

Using the analogy of a prolonged Q-Tc as evidence of active carditis (Taran and Szilagyi, 1947), or cardiac enlargement from any cause (van Lingen, 1947), we can regard our observations of a

prolonged Q-Tc in 18 out of 26 patients as further evidence of myocardial toxicity produced by 'astiban'.

We believe that the high incidence of sinus arrhythmia and bifid P waves of normal duration and height can be explained as normal variations. A high take-off with elevation of the S-T segment in chest leads was reported by Powell (1959) as a normal variation in Bantu African subjects from South Africa. Whether one accepts Powell's explanation or regards the tracing as an artefact produced by the Cambridge direct writing machine seems to us immaterial as the phenomenon could not be attributed to 'astiban'.

SUMMARY

Thirty-four patients with intestinal schistosomiasis were treated with a 5 day course of 2 G of 'astiban' given by daily intramuscular injections. Pre- and immediately post-treatment electrocardiograms in 26 patients revealed a high incidence of T wave changes usually with prolongation of Q-Tc. 'Astiban' is cardiotoxic but our findings confirm that it is less toxic than SAT.

We wish to thank the medical staff of the Mulago Hospital and Luzira Prison Hospital for referring patients for treatment and the Chief Medical Officer, Ministry of Health, Uganda, for facilities at Mulago Hospital. We are grateful to Dr. E. A. H. Friedheim and Messrs. Hoffman-La Roche for generous supplies of 'astiban'.

Since this paper was submitted for publication another report on the electrocardiographic effects of antimony dimercapto-succinate has been published (Davis, A., 1961, *Brit. Heart J.*, 23, 291).

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